Palladium Catalyzed Synthesis of Phenylquinoxaline-Alkyne Derivatives *via* Sonogashira Cross Coupling Reaction

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Summary: Transition metals mediated cross coupling methodologies provide an extremely powerful versatile pathway in organic syntheses undoubtedly, a facile route for syntheses and derivatization of biologically important heterocycles from easily available precursors. Sonogashira coupling reaction, a leading method to C_{sp}-C_{sp2} bond formation is one of the most important and rapid pathways to couple aryl/vinyl halides with terminal alkynes. Current research study deals with the synthesis of alkyne substituted quinoxaline derivatives. The quinoxalines class of aromatic heterocycles exhibits a wide variety of important biological potencies. Palladium catalyzed cross coupling process provided an effective synthetic practice for the synthesis of alkyne derivatives of quinoxaline. Vareity of terminal alkynes were coupled with 2-(4-bromophenyl)quinoxaline under optimized conditions for Sonogashira reaction, affording alkyne substituted quinoxaline derivatives in high yields. The optimized reaction conditions for coupling of range of terminal alkyne with quinoxaline basic core render this process significant for designing of medicinally interesting precursors.

Keywords: Quinoxaline, Sonogashira coupling, palladium catalysis, alkyne, heterocyclic derivatives

Introduction

Quinoxaline **1a** is a fascinating class of nitrogen containing heterocyclic compounds also known as benzopyrazines having a broad spectrum of biological applications. In pharmaceuticals, quinoxalines serve as building blocks of many drugs and exhibit a wide-ranging of antimicrobial activities [1, 2]. A natural source of quinoxaline is riboflavin **1b**, also known as vitamin B_2 which possess an important role in energy production in the electron transport chain, fatty acid metabolism, antibody production and red blood cell formation [3]. Another example of naturally occurring quinoxaline is antibiotics echinomycin **1c**, isolated from *Streptomyces echinamatus.* Echinomycin exhibit cytotoxic effects against tumour cells and also activity against gram-positive bacteria [4].

Similarly, the synthetic class of quinoxaline derivatives showed many exciting biological activities. A new series of quinoxaline derivatives were screened against Gram-positive *Bacillus subtilis* and *Staphylococcus aureus.* Among them, compound **1d** showed promising antimicrobial activities [5]. Similarly, compound **1e**, possess very high growth inhibition values against *Mycobacterium tuberculosis* [6]. In addition, indole-quinoxaline derivative exhibits antiviral activity. The mechanism of action for the derivative **1f** has the capability to inhibit DNA/RNA replication of the virus in tissue culture and showed improved inhibitory activity against HSV (Fig 1) [7].

Due to their broad spectrum of important activities, the quinoxaline derivatives pose a suitable stake for biologically active compounds. Due to immense importance of transition metal-catalyzed reaction in syntheses and derivatization of the heterocyclic system [8-10]. Herein, we plan to derivatize quinoxaline basic core through Sonogashira cross-coupling reaction, in which an *sp and* sp^2 hybridized carbon of alkyne and aryl halide were coupled respectively [11-13]. The reaction requires a bi-metallic catalytic system; a copper source to activate terminal alkyne followed by trans-metalation to palladium catalyst with an aryl halide leading to C-C bond formation. The common side product associated with the reaction is the homocoupled product from the alkyne. However, careful reaction optimization may serve to overcome the homocoupling problem [14]. Recently, there have been much advancement in the field of heterogenous catalysis for Sonogashira reaction, paving the path for reusable and industrial applications [15-17].

Experimental

Analytical grade chemicals and solvents were utilized, and additional purification were performed when necessary. Progress of the reaction was monitor with TLC. UV light (254 nm) was used to visualize UV visible spots whereas different staining reagents *i.e.* phosphomolybdic acid, potassium permanganate, ninhydrin or anisaldehyde solution were used for visualization for UV inactive

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spots. Silica gel was used to purify the product via Flash column chromatography. Microwave experiment was performed with Dawlance microwave oven, model no. DW-180G, working at power source of 50 Hz, input power of 1400 W and microwave frequency of 2450 MHz. IR spectra were recorded on Schimadzu Fourier Transform Infra-Red Spectrophotometer model 270 using ATR (Attenuated total reflectance) facility. EIMS was determined on Agilent GCMS instrument, with GC unit model 6890N and J & W Scientific column catalogue number 122-5536 and MS model 5973 inert. The ramp temperature was 120-180 ˚C and flow rate of 1.5 mL/min. Mass spectrometric (HRMS) experiments were carried out on Finnigan MAT-311A (Germany) mass spectrometer with (ESI) ionization techniques. NMR analyses for the final products were recorded using Bruker NMR spectrophotometer (^{1}HNMR at 300 MHz and ^{13}CNMR at 75 MHz) and TMS as a reference and the values are given in units δ in ppm and J in Hz.

Synthesis of Quinoxaline

A Pyrex glass vial containing *o*-phenylenediamine (410 mg, 3.80 mmol, 210 mol %), 4-bromophenacyl bromide (500 mg, 1.81 mmol, 100 mol %) and 2-picoline (505 mg, 5.44 mmol, 300 mol%) was exposed to microwave irradiation for 30 sec (three pulses of 10 sec each) as a neat reaction, the extent of the formation of product was examined using TLC. As the reaction was completed, ethyl acetate (20 mL) was added and is washed with water (15 mL x 2). The combined organic solution was dried over $MgSO_4$ and crude product was obtained upon concentrating under vacuum. The product 2-(4-bromophenyl)quinoxaline **2** was purified through column chromatography (60 F_{254} Silica gel, n-hex: EtOAc 9.5 : 0.5), isolated in 45% yield as yellow solid. The analytical data was in accordance with the data reported in the literature [18].

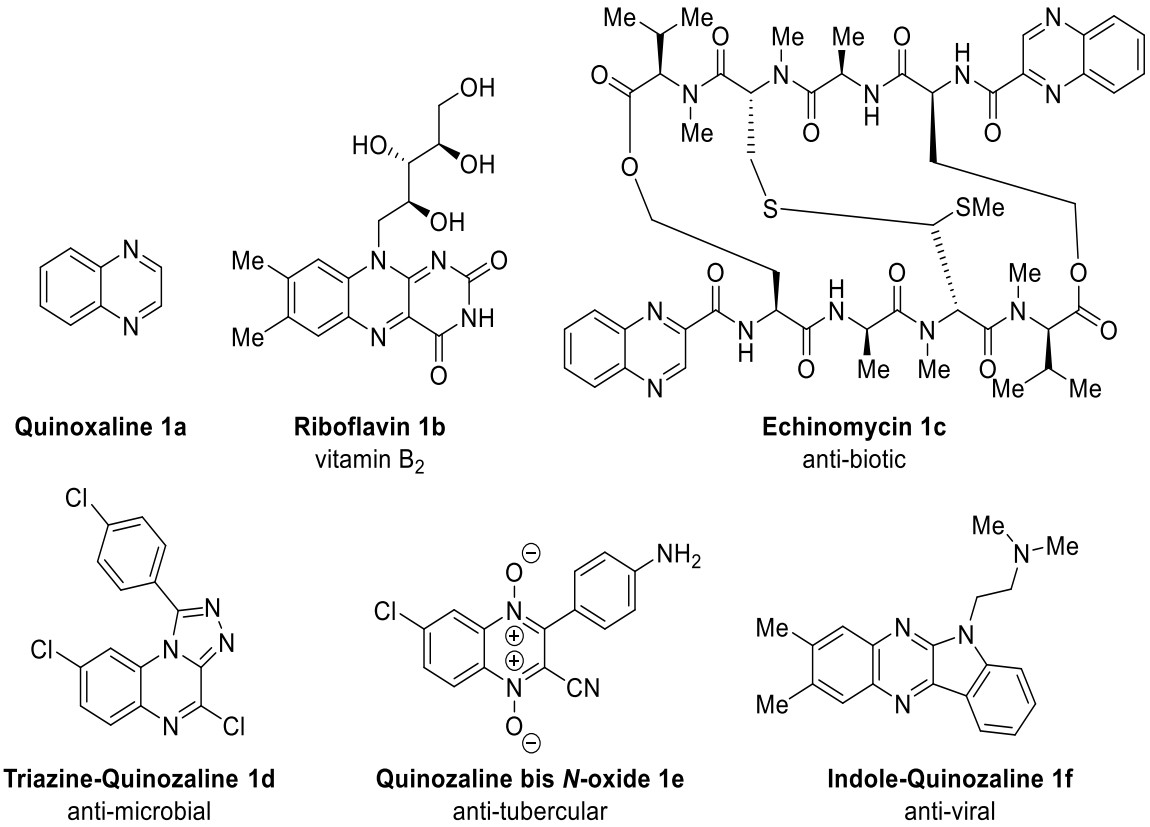
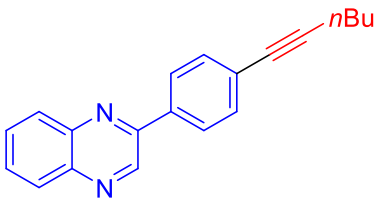


Fig. 1: Biologically important naturally and synthetic quinoxaline derivatives.

Procedure for the Sonogashira Coupling

To an oven dried sealed tube having Teflon coated stirring bead, 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol%), phenylacetylene (0.528 mmol, 150 mol%), triethylamine (0.704 mmol, 200 mol%), $(PPh_3)_2PdCl_2$ (0.007 mmol, 2 mol%) copper iodide (0.035 mmol, 10 mol%) and DMF (0.5 M) were added. Then the sealed tube was properly placed in a oil bath at 80 °C and the reaction was stirred for 24 h. Water (5 mL) was added to the mixture and extracted with EtOAc (10 mL x 3). The combine ethyl acetate layer was dried using $MgSO_4$ and concentrated under high vacuum. Pure products **4a** – **4f** were obtained using column chromatography (SiO_2: *n*-Hex: EtOAc 9.5 : 0.5).

Synthesis of 2-(4-(hex-1-ynyl) phenyl)quinoxaline **(4a)**



The reaction was performed using 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol %), 1-hexyne **3a** (0.528 mmol, 150 mol%), Et_3N (0.704 mmol, 200 mol%), $PdCl_2(PPh_3)_2$ (0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol %) in DMF (0.5 M).

Yield: 72%, dark brown solid, R_f = 0.41 (*n*-Hex: EtOAc, 9:1).

^{1}HNMR (300 MHz, $CDCl_3$): 9.33 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 8.17 - 8.11 (m, 2H), 7.80-7.50 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.68 - 1.61 (m, 2H), 1.59 - 1.47 (m, 2H), 0.99 (t, *J* = 7 Hz, 3H) ppm.

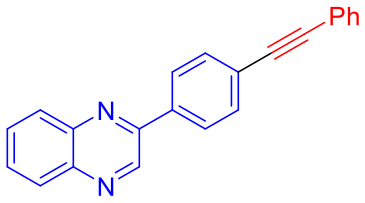
^{13}CNMR (75 MHz, $CDCl_3$): 151.1, 143.1, 142.3, 141.6, 135.5, 132.3, 130.4, 129.64, 129.6, 129.1, 127.3, 126.2, 93.0, 80.3, 30.8, 22.1, 19.3, 13.7 ppm.

EI MS (m/z): 286, 271, 257, 243, 140, 129, 76.

HR ESI MS (m/z): $[M+H]^+$ calculated for $C_{20}H_{19}N_2^+$ 287.1543, found 287.1546.

IR (cm^{-1}): 2946, 2929, 2855, 2204, 1563, 1479, 1452, 1384, 1364, 1331, 1245, 1223, 1206, 1134, 1027, 989, 754, 712, 607, 503.

Synthesis of 2-(4-(2-phenylethynyl)phenyl)quinoxaline **(4b)**



The reaction was performed using 2-(4-bromo phenyl) quinoxaline **2** (0.352 mmol, 100 mol %), phenylacetylene **3b** (0.528 mmol, 150 mol%), Et_3N (0.704 mmol, 200 mol %) $(PPh_3)_2PdCl_2$ (0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol %) in DMF (0.5 M).

Yield: 61%, yellow solid, R_f =0.32 (*n*-Hex : EtOAc, 9:1).

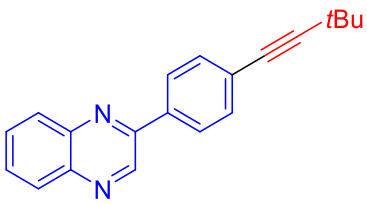
^{1}HNMR (300 MHz, $CDCl_3$): 9.33 (s, 1H), 8.24 (d, *J* = 9.0 Hz, 2H), 8.19 - 8.12 (m, 2H), 7.81 - 7.76 (m, 2H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.60 - 7.40 (m, 5H) ppm.

^{13}CNMR (75 MHz, $CDCl_3$): 150.9, 143.1, 142.3, 141.6, 136.3, 132.3, 131.7, 130.4, 129.8, 129.6, 129.2, 129.0, 128.6, 127.4, 125.3, 122.9, 91.6, 89.0 ppm.

HR ESI MS (m/z): $[M+H]^+$ calculated for : $C_{22}H_{15}N_2^+$ 307.1230, found 307.1234.

IR (cm^{-1}): 2973, 2214, 1573, 1559, 1494, 1446, 1384, 1353, 1342, 1214, 1139, 1120, 1007, 751, 689.

Synthesis of 2-(4-(3, 3-dimethyl-1-butynyl)phenyl)quinoxaline **(4c)**



The reaction was performed using 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol %), 3,3-dimethylbut-1-yne **3c** (0.528 mmol, 150 mol%), Et_3N (0.704 mmol, 200 mol %) $(PPh_3)_2PdCl_2$

(0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol %) in DMF (0.5 M).

Yield: 61%, yellow solid, R_f = 0.32 (*n*-Hex : EtOAc, 9:1).

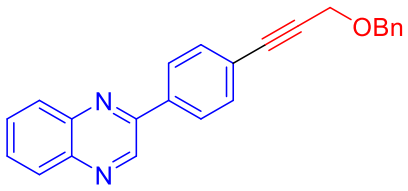
^{1}HNMR (300 MHz, $CDCl_3$): 9.30 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 8.16 - 8.09 (m, 2H), 7.78 - 7.73 (m, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 1.38 (s, 9H) ppm.

^{13}CNMR (75 MHz, $CDCl_3$): 151.0, 143.1, 142.3, 141.6, 135.4, 132.3, 130.3, 129.6, 129.1, 127.2, 126.2, 101.0, 78.8, 31.0, 28.0 ppm.

HR ESI MS (m/z): $[M+H]^+$ calculated for : $C_{20}H_{19}N_2^+$ 287.1543, found 287.1548.

IR (cm^{-1}): 2941, 2926, 2845, 2208, 1562, 1473, 1459, 1386, 1369, 1333, 1248, 1221, 1209, 1133, 1024, 981, 759, 714, 608, 503.

Synthesis of 2-(4-(3-(benzyloxy)prop-1-ynyl)phenyl)quinoxaline **(4d)**



The reaction was performed using 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol%), 1-((prop-2-ynyloxy)methyl)benzene **3d** (0.528 mmol, 150 mol%), Et_3N (0.704 mmol, 200 mol%), $(PPh_3)_2PdCl_2$ (0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol%) in DMF (0.5 M).

Yield: 67%, yellow gummy solid, R_f = 0.35 (*n*-Hex : EtOAc 9:1).

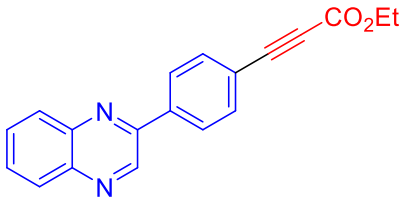
^{1}HNMR (300 MHz, $CDCl_3$): 9.35 (s, 1H), 8.20 (d, *J* = 9.0 Hz, 2H), 8.19 - 8.13 (m, 2H), 7.82 - 7.77 (m, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.46 - 7.34 (m, 5H), 4.70 (s, 2H), 4.47 (s, 2H) ppm.

^{13}CNMR (75 MHz, $CDCl_3$): 150.1, 143.1, 142.3, 141.6, 137.4, 136.6, 132.5, 130.5, 129.8, 129.6, 129.2, 128.5, 128.2, 128.0, 127.4, 124.6, 114.0, 87.4, 71.9, 58.0 ppm.

HR ESI MS (m/z): $[M+H]^+$ calculated for: $C_{24}H_{19}N_2O^+$ 351.1492, found 351.1495.

IR (cm^{-1}): 3281, 3014, 2959, 2918, 2218, 1575, 1569, 1454, 1371, 1337, 1227, 1209, 1129, 1051, 1011, 959, 766, 659, 624.

Ethyl-3-(4-(quinoxalin-2-yl)phenyl)propiolate **(4e)**



The reaction was performed using 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol%), ethyl propiolate **3e** (0.528 mmol, 150 mol%) in presence of Et_3N (0.704 mmol, 200 mol%), $(PPh_3)_2PdCl_2$ (0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol%) in DMF (0.5 M).

Yield: 47%, yellow gummy solid, R_f = 0.36 (*n*-Hex: EtOAc 9:1).

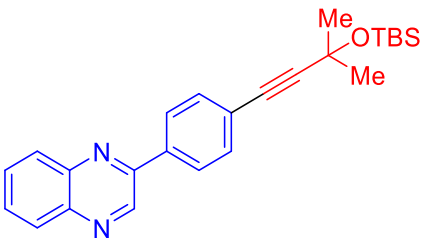
^{1}HNMR (300 MHz, $CDCl_3$): 9.30 (s, 1H), 8.16 - 8.11 (m, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.8 - 7.75 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}CNMR (75 MHz, $CDCl_3$): 167.9, 150.9, 143.1, 142.3, 141.6, 136.3, 132.8, 132.3, 129.7, 129.6, 129.2, 129.0, 122.9, 88.7, 82.1, 60.1, 13.2 ppm.

HR ESI MS (m/z): $[M+H]^+$ calculated for: $C_{19}H_{15}N_2O_2^+$ 303.1128, found 303.1132.

IR (cm^{-1}): 3208, 2941, 2913, 2241, 1741, 1564, 1515, 1442, 1381, 1345, 1221, 1203, 1141, 1036, 959, 761, 649, 624, 511.

(2-Methyl-4-(4-(quinoxalin-2-yl)phenyl)-3-butyn-2-yloxy)(tert-butyl)dimethylsilane **(4f)**



The reaction was performed using 2-(4-bromophenyl)quinoxaline **2** (0.352 mmol, 100 mol%), (2-methylbut-3-yn-2-yloxy)(tert-

butyl)dimethylsilane **3f** (0.528 mmol, 150 mol%), Et_3N (0.704 mmol, 200 mol%) $(PPh_3)_2PdCl_2$ (0.007 mmol, 2 mol%), CuI (0.035 mmol, 10 mol%) in DMF (0.5 M).

Yield: 98%, yellow gummy solid, R_f = 0.43 (*n*-Hex : EtOAc, 9:1).

^{1}HNMR (300 MHz, $CDCl_3$): 9.34 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.19 - 8.13 (m, 2H), 7.82 - 7.77 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 1.61 (s, 6H), 0.93 (s, 9H), 0.26 (s, 6H) ppm.

^{13}CNMR (75 MHz, $CDCl_3$): 151.0, 143.1, 142.3, 141.6, 136.1, 132.1, 130.4, 129.8, 129.6, 129.2, 127.4, 125.2, 97.1, 82.2, 66.7, 32.9, 25.8, 18, -2.9 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for: $C_{25}H_{31}N_2OSi^+$ 403.2200, found 403.2203.

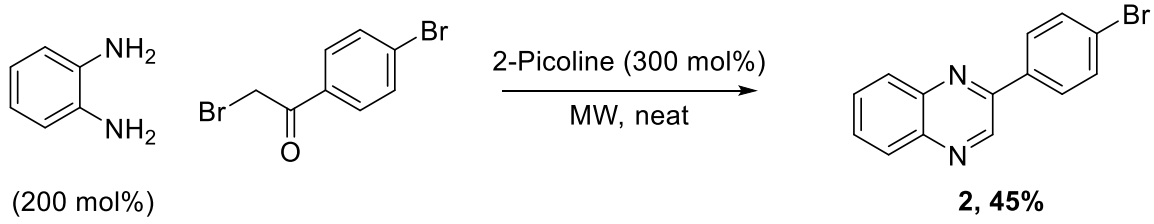
IR (cm^{-1}): 3289, 3011, 2969, 2938, 2239, 1572, 1552, 1451, 1371, 1335, 1229, 1201, 1149, 1081, 1023, 951, 769, 652.

Result and Discussion

The substrate 2-(4-bromophenyl)quinoxaline **2** was prepared using a modified method utilizing microwave irradiation of the neat mixture of *o*-phenylenediamine, *p*-bromophenacyl bromide, and 2-picoline [8, 19]. The purified product was obtained through column chromatography in 45% yield as yellow solid. The bromophenyl substituted quinoxaline serves as a position for further derivatization.

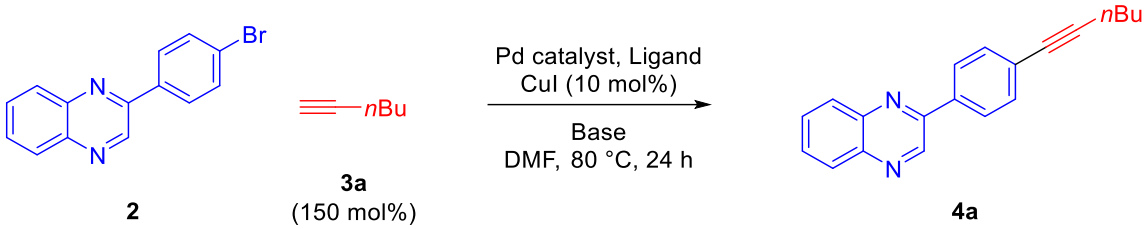
The quinoxaline derivative **2** was reacted with a variety of alkynes under palladium catalysis. Standard reaction conditions for Sonogashira reaction were utilized [14]. Initially, 5 mol% palladium acetate in conjunction with triphenylphosphine was utilized as the catalytic system in DMF as solvent [20]. while using potassium carbonate as a base afforded product **4a** after column purification (Table 1 entry 1). Further optimization was performed by changing different parameters and selected reactions are shown in Table 1. Therefore, by changing to tetrakis(triphenylphosphine)palladium as catalyst under otherwise similar condition, the product **4a** was isolated in 56% isolated yield. Since tetrakis(triphenylphosphine)palladium is a palladium(0) complex, it can be presumed that it will be easy for the palladium to enter to catalytic cycle and may improve the yield, however, no improvement was observed (Table 1 entry 2). On the contrary, using bis(triphenylphosphine)palladium chloride as catalyst result in a slight increase in the yield, while changing to triethylamine as a base, the product was isolated in 73% yield (Table 1 entries 3 and 4). However, changing to THF considerably lower the yield to 57%. Using any other solvent did not improve the reactivity. To our delight, using the best condition and lowering the bis(triphenylphosphine)palladium chloride catalyst loading to only 2 mol% did not affect the yield (Table).

Once we had the optimized conditions for Sonogashira coupling for quinoxaline, the reaction was performed with various terminal alkynes. When reaction was performed with phenylacetylene, product **4b** was isolated in 61% yield. Similarly, *tert*-butylacetylene showed similar reactivity and resulted in the coupled alkyne **4c** in 61% isolated yield. Propargyl benzyl ether and ethyl propiolate smoothly underwent Sonogashira coupling afforded the product **4d** in 67% and **4e** in 47% isolated yield. The lower yield with ethyl propiolate may be attributed to its inferior reactivity. Finally, TBS protected 2-methyl-3-butyn-2-ol resulted the product **4f** in 98% yield (Table 2).



Scheme-1: Synthesis of 2-(4-bromophenyl)quinoxaline **2**.

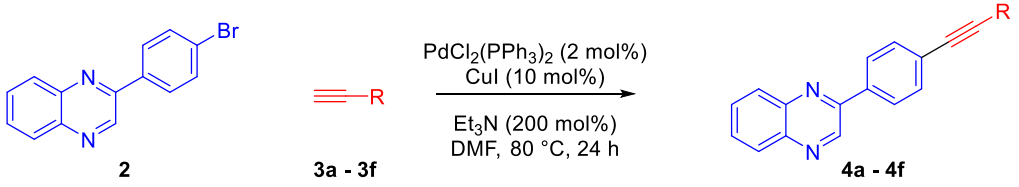
Table-1: Reaction condition for Sonogashira coupling of quinoxaline.



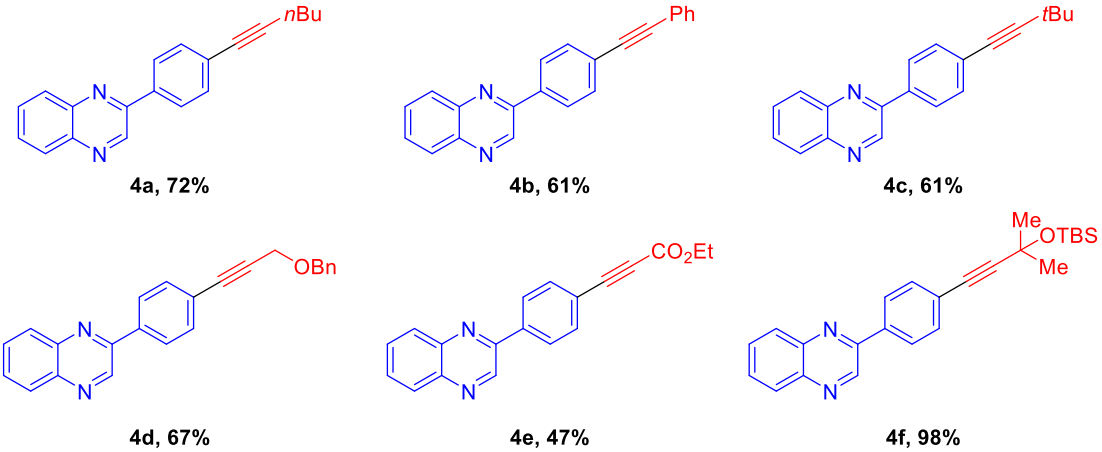
2 **3a** (150 mol%) **4a**

S. NO.	Pd Source	Ligand	Base	Solvent	Yield (%)
1	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	K_2CO_3	DMF	54
2	$Pd(PPh_3)_4$ (5 mol%)	–	K_2CO_3	DMF	56
3	$PdCl_2(PPh_3)_2$ (5 mol%)	–	K_2CO_3	DMF	59
4	$PdCl_2(PPh_3)_2$ (5 mol%)	–	Et_3N	DMF	73
5	$PdCl_2(PPh_3)_2$ (5 mol%)	–	Et_3N	THF	57
6	$PdCl_2(PPh_3)_2$ (2 mol%)	–	Et_3N	DMF	72

Table-2: Sonogashira coupling of quinoxaline with variety of alkynes.



2 **3a - 3f** (150 mol%) **4a - 4f**



4a, 72% **4b, 61%** **4c, 61%**

4d, 67% **4e, 47%** **4f, 98%**

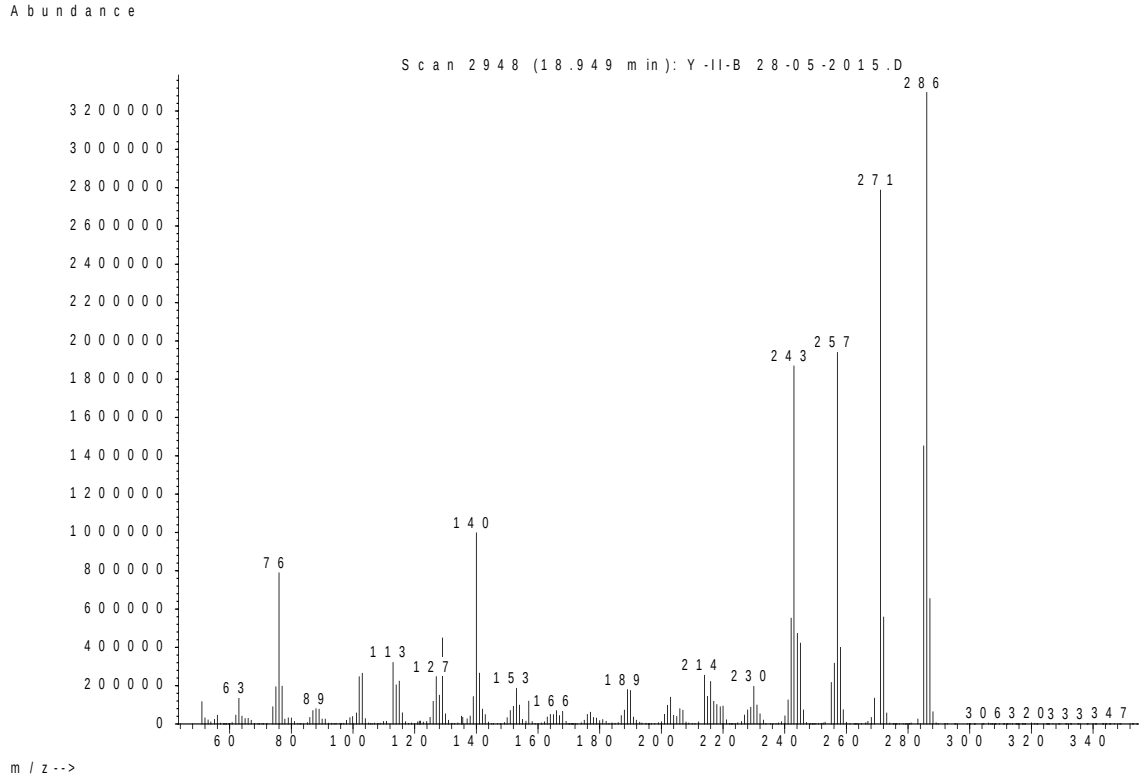
Representative NMR Analysis 2-(4-(Hex-1-ynyl)phenyl)quinoxaline **(4a)**

In the ^{1}HNMR spectrum, the singlet at 9.33 ppm corresponds to one proton of pyrazine ring. This signal appears downfield as compared with other aromatic protons due to effect of two nitrogen atoms in the ring. Multiplets at 8.17 - 8.11 and 7.80 - 7.50 ppm are due to the two remaining aromatic nuclei. Two doublets (each for two protons) at 8.16 ppm (J = 8.0 Hz) and 7.60 ppm (J = 8.0 Hz) remain consistent with pattern of signals in *p*-disubstituted aromatic ring. Triplet of two protons at 2.48 ppm (J = 7.0 Hz) is assign to methylene α to alkyne functionality. Signals at 1.68 - 1.61 and 1.59 - 1.47 ppm appear as multiplets are exhibited by two sets of β- and γ-methylene protons. Terminal methyl group showed a triplet signal at 0.99 ppm.

In ^{13}C-NMR spectrum, peak at 151.1 ppm is attributed to phenyl substituted carbon of quinoxaline. A signal at 143.1 ppm is due to carbon 3 of quinoxaline moiety. Signals at 142.3 and 141.6 ppm are due to bridge head carbons. One carbon of alkyne moiety appears at 93.0 ppm and other carbon directly attached with *p*-substituted phenyl exhibit signal at 80.3 ppm. Signals at 30.8 and 22.1 ppm are due to β and γ carbons of methylene groups respectively. Methylene carbon α to alkyne moiety showed a signal at 19.3 ppm. Carbon nuclei of the terminal methyl group showed a signal at 13.7 ppm.

Mass Spectrometry Fragmentation Pattern for 2-(4-(Hex-1-ynyl)phenyl)quinoxaline **(4a)**

The molecular ion peak was at m/z = 286 confirms the synthesis of product **4a**. Interestingly, incremental peaks of m/z = 271, 257 and 243 are due to the subsequent loss of methyl group, ethyl group and propyl group from the parent structure. This is a characteristic fragmentation pattern of the alkyl chain due to methylene loss (14 mass units). Quinoxaline fragment showed a peak at m/z = 129. A signal at m/z = 76 is exhibited by *p*-disubstituted phenylene or benzyne (Fig. 2)



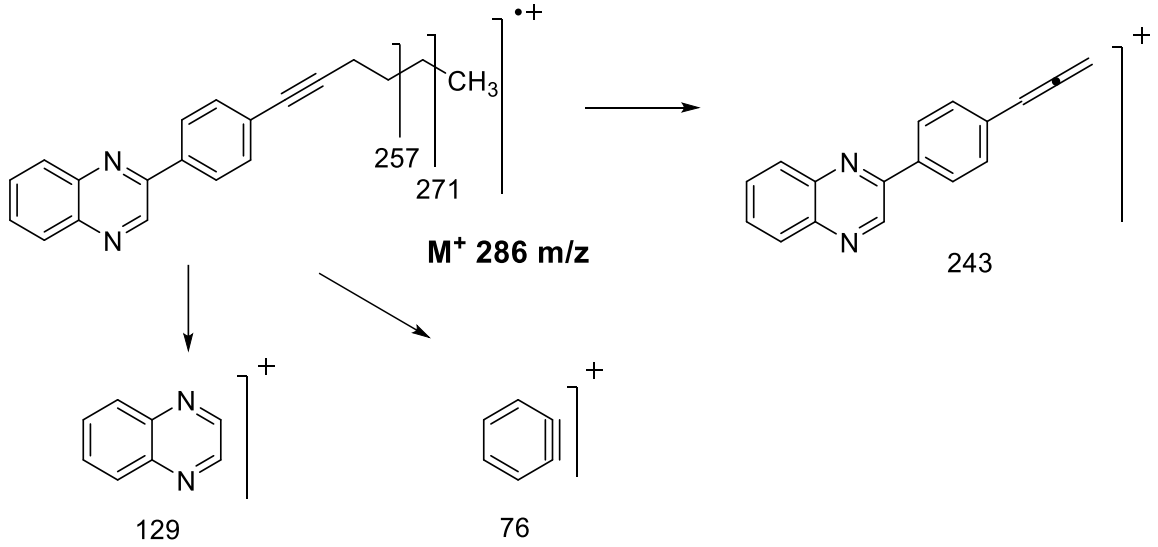


Fig. 2: EI-MS of compound 4a and proposed fragmentation pattern of compound 4a according to EI-MS.

Conclusion

The current research deals with optimization and utilization of Pd-catalyzed Sonogashira coupling methodology for the syntheses of unsaturated quinoxaline derivatives by coupling of variety of alkynes with quinoxaline phenylbromide. The general reaction conditions utilized for this coupling reaction were obtained by optimizing various reaction parameters using a coupling of 1-hexyne with 2-(4-bromophenyl)quinoxaline **2** as a model substrate. The reaction was optimized in term of catalyst, catalyst loading, base and solvent used. The optimized reaction conditions obtained, were the use of co-catalyst *i-e* $PdCl_2(PPh_3)$ (2mol%) and CuI (10mol%), Et_3N (200mol%) as base in DMF solvent (0.5M) heated at 80 ^oC for 24 hrs. The reaction scope were evaluated by coupling range of terminal alkyne with 2-(4-bromophenyl)quinoxaline **2** under optimized reaction conditions, resulting in alkyne substituted quinoxaline derivatives in delightful yields. Coupled products were identified and analyzed with various chromatographic and spectroscopic techniques. The synthetic utility of the developed reaction conditions for Sonogashira coupling maybe extended for the reaction of heteroaryl halide and functionalized alkynes to provide a new strategy for the construction of alkyne substituted moieties.

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